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Effect of indomethacin on the renal response to angiotensin II receptor blockade in healthy subjects

ANNE F. FRICKER, JÜRG NUSSBERGER, SUSANNE MEILENBROCK, HANS R. BRUNNER, and MICHEL BURNIER

Division of Hypertension and Vascular Medicine, University Hospital, Lausanne, and Novartis, Basel, Switzerland

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Background. Non-steroidal anti-inflammatory drugs are known to promote sodium retention and to blunt the blood pressure lowering effects of several classes of antihypertensive agents including beta-blockers, diuretics and angiotensin converting enzyme (ACE) inhibitors. The purpose of the present study was to investigate the acute and sustained effects of indomethacin on the renal response to the angiotensin II receptor antagonist valsartan and to the ACE inhibitor enalapril.

Methods. Twenty normotensive subjects maintained on fixed sodium intake (100 mmol sodium/day) were randomized to receive for one week: valsartan 80 mg o.d., enalapril 20 mg o.d., valsartan 80 mg o.d. + indomethacin 50 mg bid and enalapril 20 mg o.d. + indomethacin 50 mg bid. This single-blind study was designed as a parallel (valsartan vs. enalapril) and cross-over trial (valsartan or enalapril vs. valsartan + indomethacin or enalapril + indomethacin). Renal hemodynamics and urinary electrolyte excretion were measured for six hours after the first and seventh administration of each treatment regimen.

Results. The results show that valsartan and enalapril have comparable renal effects characterized by no change in glomerular filtration rate and significant increases in renal plasma flow and sodium excretion. The valsartan- and enalapril-induced renal vasodilation is not significantly blunted by indomethacin. However, indomethacin similarly abolishes the natriuresis induced by the angiotensin II antagonist and the ACE inhibitor.

Conclusions. This observation suggests that although angiotensin receptor antagonists do not affect prostaglandin metabolism, the administration of a non-steroidal anti-inflammatory drug blunts the natriuretic response to angiotensin receptor blockade.

The renin-angiotensin system and renal prostaglandins are two important factors contributing to the control of renal hemodynamics and urinary electrolyte excretion [1]. Angiotensin II modulates renal perfusion and glomerular filtration rate through its effects on renal arterioles and glomerular mesangial cells [2]. Angiotensin II also has a direct effect on proximal tubular sodium reabsorption and an indirect influence on sodium handling by the distal tubule via its ability to stimulate the release of aldosterone [2, 3]. Lastly, angiotensin II exerts a negative feedback on renin release. The renal prostaglandins tend to counterbalance the vasoconstrictor and antinatriuretic effects of angiotensin II, promoting a renal vasodilation and sodium excretion through their effects on renal arterioles and medullary blood flow and their influence on tubular sodium reabsorption [1, 4]. In addition, the release of renin from juxtamedullary cells is modulated by the synthesis of prostaglandin I_2 [1]. The renal homeostatic role of prostaglandins becomes particularly important in conditions of salt and/or water depletion that is, when vasoconstrictor systems are stimulated.

Clinically, the co-administration of non-steroidal anti-inflammatory drugs (NSAIDs) and antihypertensive agents often results in blunting of the effect of antihypertensive therapy [5, 6]. The mechanism of this drug interaction appears to involve the inhibition of vascular and renal prostaglandin synthesis leading to vasoconstriction and sodium retention [5]. The risk of interaction is greatest in elderly and low-renin hypertension, and occurs most frequently with the use of diuretics, beta-blockers and ACE-inhibitors. No interaction has been reported with centrally-acting alpha agonists and calcium channel blockers [6–8]. Because ACE inhibitors such as captopril have been found to stimulate the production of prostaglandins *in vitro* as well as *in vivo*, it has been proposed that some of the renal effects of ACE inhibitors are in fact mediated by prostaglandins [9, 10]. These observations have supported the hypothesis that ACE inhibitors act not only by inhibiting angiotensin II formation, but also by preventing the degradation of bradykinin that partly acts via vasodilatory prostaglandin release.

Recently, several nonpeptide, orally-active angiotensin II receptor antagonists have been developed that specifically block the angiotensin AT_1 receptor subtype. Studies in hypertensive patients have demonstrated that these antagonists are comparable to ACE inhibitors in their ability to

Key words: NSAIDs, prostaglandins, renal function, valsartan, enalapril, ACE inhibition, hemodynamics.

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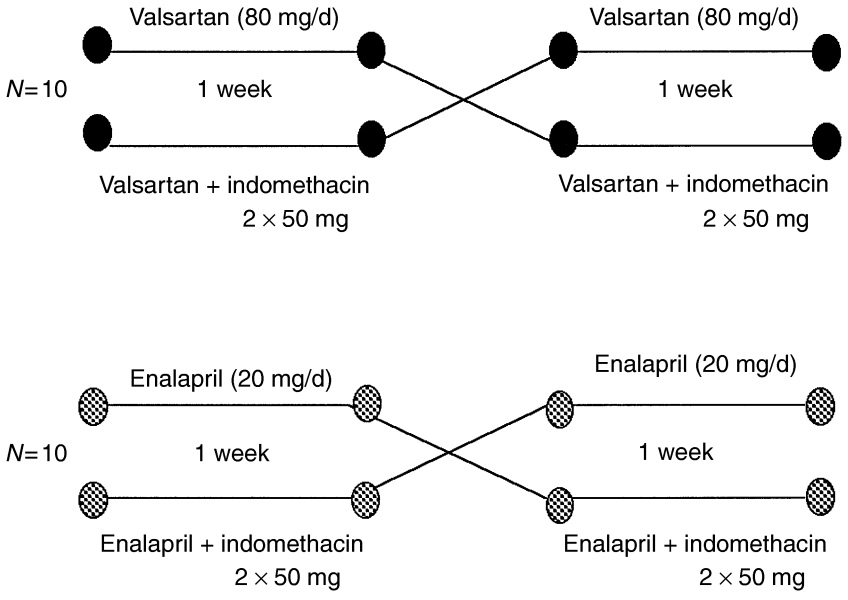

Fig. 1. Schematic representation of the study design. Ovals denote the determination of renal function.

lower blood pressure in hypertensive patients [11]. In addition, angiotensin II receptor blockade and ACE inhibition appear to have similar impacts on renal hemodynamics, sodium excretion and urinary protein excretion [12–14]. In contrast to ACE inhibitors, these antagonists block the renin-angiotensin system without interfering with the metabolism of kinins and prostaglandins [15]. Thus, if prostaglandins contribute to the renal response to ACE inhibition, this should not be the case during angiotensin II receptor blockade. Thus far, the interaction between NSAIDs and angiotensin II receptor antagonists has never been evaluated in humans.

The purpose of this study was to examine the effect of indomethacin, an inhibitor of prostaglandin synthesis, on the renal response to angiotensin II receptor blockade by valsartan and to compare it to its interaction with the ACE inhibitor enalapril. Our results demonstrate that indomethacin has no significant effect on the renal vasodilation caused by angiotensin II receptor blockade and ACE inhibition. However, indomethacin abolishes both the valsartan- and the enalapril-induced sodium excretion. This suggests that the interaction between NSAIDs and ACE inhibitors is not class-specific.

METHODS

Twenty healthy white male volunteers aged 20 to 35 years (mean 24.9 years) weighing 74.8 kg (range 60 to 94 kg) completed this study. Each volunteer had a medical history taken and underwent a complete physical examination. Their baseline systolic and diastolic blood pressures were 121.4 ± 2.0 and 76.0 ± 1.9 mm Hg, respectively (mean ± SEM). Routine laboratory tests were done before and after administration of the drug. The nature and the purpose of the study had been explained, and written informed consent had been obtained previously from each subject. The protocol was approved by the Hospital Ethics Committee (CHUV, Lausanne, Switzerland).

Study design

The study was designed as a parallel and crossover trial with valsartan (80 mg) and valsartan (80 mg) + indomethacin (50 mg bid) in one arm and enalapril (20 mg) and enalapril (20 mg) + indomethacin (50 mg bid) in the other arm (Fig. 1). The two treatment phases each lasted seven days and were separated by a one-week washout period. Ten subjects were randomized to receive valsartan and valsartan + indomethacin and 10 other subjects received enalapril and enalapril + indomethacin. To reduce intersubject variability, the subjects were studied while they were on a fixed sodium diet containing 100 mmol sodium and 3500 calories per day. The diet began one week before drug administration and was maintained throughout the study, that is, for 28 days. The diet was provided, under the supervision of a dietician, by the hospital restaurant where the subjects ate all their meals. Diet compliance was evaluated by repeated 24-hour urine collections.

On day 1 (after at least 1 week of diet), the volunteers came to the hospital at 7 a.m. after an overnight fast to undergo clearance studies. Upon arrival, they were made comfortable on a bed. They remained supine, except for voiding, and fasted throughout the study procedure. Two intravenous catheters were inserted into antecubital veins, one for the infusion of inulin and para-aminohippurate (PAH) in a glucose/saline solution and a second one into the contralateral forearm for blood drawing.

Between 7:00 and 8:00 a.m., the volunteers drank an oral water load of 5 ml/kg. After a priming dose, the i.v. infusion

Table 1. Acute (day 1) hemodynamic and tubular effects of indomethacin during angiotensin II receptor blockade and angiotensin converting enzyme (ACE) inhibition

Parameter	Valsartan		Valsartan + Indomethacin		Enalapril		Enalapril + indomethacin	
	T0	T4	T0	T4	T0	T4	T0	T4
SBP *mm Hg*	109 ± 2.6	112 ± 2.6	108 ± 2.3	111 ± 1.9	107 ± 2.2	104 ± 2.2	109 ± 2.3	106 ± 3.2
DBP *mm Hg*	73 ± 1.5	56 ± 2.5[b]	70 ± 2.2	63 ± 2.9[a]	68 ± 2.6	59 ± 3.1[b]	69 ± 1.5	62 ± 2.7[b]
HR *bpm*	56 ± 2.7	67 ± 4.0	57 ± 1.8	63 ± 2.3	60 ± 2.7	72 ± 4.7	63 ± 3.1	68 ± 3.9
GFR *ml/min/1.73 m²*	121 ± 6.2	117 ± 7.6	121 ± 7.8	119 ± 9.4	124 ± 8.0	120 ± 8.1	128 ± 6.1	126 ± 6.2
ERPF *ml/min/1.73 m²*	540 ± 42	598 ± 34	558 ± 52	581 ± 65	580 ± 38	637 ± 34	622 ± 33	639 ± 47
FF *%*	23.1 ± 1.2	19.9 ± 1.4	23.4 ± 2.3	21.9 ± 2.1	21.8 ± 1.1	18.9 ± 0.8[a]	20.9 ± 0.1	20.4 ± 1.3
$U_{Na}V$ *μmol/min*	107 ± 16	176 ± 23[a]	101 ± 18	103 ± 12.2	143 ± 16	181 ± 18[a]	154 ± 22.9	111 ± 16.2
U_KV *μmol/min*	80.2 ± 8.0	55.6 ± 5.8[b]	77.7 ± 9.3	59.3 ± 6.8[a]	71.2 ± 7.8	36.4 ± 4.8[b]	73.3 ± 6.1	43.7 ± 5.9[b]
FE_{Na} *%*	0.69 ± 0.10	1.28 ± 0.13[a]	0.68 ± 0.10	0.68 ± 0.06	0.99 ± 0.14	1.28 ± 0.14[a]	0.99 ± 0.13	0.73 ± 0.11
FE_K *%*	17.8 ± 1.8	14.5 ± 1.4	18.4 ± 2.4	14.1 ± 1.5	16.8 ± 2.0	9.0 ± 0.9	16.5 ± 1.3	9.8 ± 1.1
FE_{Li} *%*	25.7 ± 2.0	21.4 ± 1.6	23.6 ± 1.8	17.6 ± 1.2[b]	26.9 ± 2.5	22.8 ± 1.6	26.3 ± 3.8	20.2 ± 2.3

Abbreviations are: SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; GFR, glomerular filtration rate; ERPF, effective renal plasma flow; and FF, filtration fraction. U_xV, urinary excretion of x in micromoles per minute; FE_x, fractional excretion of x or clearance of x divided by glomerular filtration rate. T0 and T4 indicate baseline value and value 4 hours after drug intake, respectively.

[a] $P < .05$

[b] $P < .01$ vs. T0

Table 2. Sustained (day 7) hemodynamic and tubular effects of indomethacin during angiotensin II receptor blockade and ACE inhibition

Parameter	Valsartan		Valsartan + Indomethacin		Enalapril		Enalapril + Indomethacin	
	T0	T4	T0	T4	T0	T4	T0	T4
SBP *mm Hg*	105 ± 1.6	110 ± 2.3	103 ± 2.7	112 ± 3.3	104 ± 2.3	104 ± 1.8	105 ± 0.9	107 ± 2.7
DBP *mm Hg*	69 ± 1.5	62 ± 2.3	68 ± 2.1	63 ± 3.0	66.1 ± 2.7	54 ± 3.0	66 ± 1.9	57 ± 2.3
HR *bpm*	56 ± 1.7	68 ± 3.0	55 ± 1.3	65 ± 3.3	60 ± 3.3	71 ± 3.1	61 ± 2.9	68 ± 3.8
GFR *ml/min/1.73 m²*	119 ± 6.9	119 ± 6.9	118 ± 7.9	117 ± 12.0	114 ± 8.6	115 ± 6.9	123 ± 7.0	112 ± 7.3
ERPF *ml/min/1.73 m²*	515 ± 38	644 ± 46[b]	561 ± 50	589 ± 42	562 ± 40	658 ± 41	597 ± 36	664 ± 41
FF *%*	24.6 ± 2.1	19.3 ± 1.6	22.0 ± 1.7	20.1 ± 1.7	20.5 ± 1.1	17.8 ± 1.2	20.9 ± 1.2	17.1 ± 1.0
$U_{Na}V$ *μmol/min*	64 ± 7	134 ± 14[b]	98 ± 15	80 ± 7	102 ± 19	155 ± 22[a]	136 ± 15.5	106 ± 7.3
U_KV *μmol/min*	65 ± 7.2	60 ± 9.1	76 ± 9.3	62 ± 7.4	91 ± 10.0	60 ± 5.9[b]	94 ± 14.8	48 ± 5.4[b]
FE_{Na}, *%*	0.45 ± 0.06	0.92 ± 0.11[b]	0.62 ± 0.09	0.56 ± 0.05	0.76 ± 0.15	1.11 ± 0.16[a]	0.93 ± 0.11	0.79 ± 0.07
FE_K, *%*	15.7 ± 2.1	14.7 ± 2.1	16.5 ± 1.8	15.2 ± 1.7	22.0 ± 2.3	14.5 ± 1.1	20.8 ± 3.1	11.6 ± 0.9
FE_{Li}, *%*	26.8 ± 2.6	24.6 ± 2.8	23.0 ± 1.8	20.9 ± 2.1	29.8 ± 2.5	26.3 ± 2.1	24.3 ± 2.4	19.7 ± 2.4

Abbreviations are: SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; GFR, glomerular filtration rate; ERPF, effective renal plasma flow; and FF, filtration fraction. U_xV, urinary excretion of x in micromoles per minute; FE_x, fractional excretion of x or clearance of x divided by glomerular filtration rate. T0 and T4 indicate baseline value and value 4 hours after drug intake, respectively.

[a] $P < .05$

[b] $P < .01$ vs. T0

of inulin and PAH was started; the infusions were calculated to provide plasma concentrations of approximately 400 μg/ml and 20 μg/ml, respectively. The volunteers were asked to empty their bladder every 60 minutes before drug intake and every two hours after drug intake. After each voiding, a fixed amount of water (100 ml/hr) was given orally to sustain urine output. After a two-hour equilibration period, two baseline measurements were performed until the volunteers were in steady-state. These two measurements were averaged to determine the baseline value (T0 in Tables 1 and 2). At the end of the baseline period (T0), the volunteers were randomized to receive their drug in single-blinded fashion.

Blood pressure, heart rate, urinary electrolyte excretion and clearances of inulin and PAH to assess glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were measured at one hour intervals before drug intake and at two hour intervals for six hours after drug administration. Simultaneously, blood samples were drawn for the measurement of electrolytes. Blood pressure was obtained from the patients in a supine position and was measured by the conventional auscultatory method. Blood samples for the determination of plasma renin activity were drawn after one hour in supine position in the morning of day 1 and day 7 before drug intake.

On study days 2 to 7, the morning doses of valsartan, enalapril and indomethacin were administered between 8 and 9 a.m. The evening dose of indomethacin was administered bewteen 6 and 8 p.m. Blood pressure (BP) and heart rate were measured with the patient in a supine position before the drug was given. Body weight and 24-hour urinary sodium, potassium and creatinine excretion were measured every day during drug administration. On day 7, renal clearances were repeated as on day 1.

Drugs and chemicals

Valsartan, enalapril and indomethacin were provided by Novartis, Basel, Switzerland. Inulin was purchased from Laevosan Gesellschaft (Linz, Austria) and PAH (Nephrotest, sodium salt of para-aminohippuric acid) was from Biologische Arbeitsgemeinschaft GmBH (Lich, Essen, Germany). The gluco-saline solution contained 51 mmoles Na/liter. During the clearance days, 60 to 65 mmoles of Na were infused.

Analytic methods

Plasma and urinary inulin concentrations were measured by a microadaptation of a diphenylamine procedure on a Technicon Autoanalyser [16]. PAH concentrations were determined by spectrophotometry [17]. Plasma and urinary sodium, potasssium and chloride were analyzed with selective electrodes (Hel-ISE; Beckman). Endogenous trace lithium was measured by electrothermal absorption spectrophotometry as described by Magnin et al [18]. Intraday and interday coefficient of variations for plasma lithium were 7 and 10%, respectively. For the determination of plasma renin activity (PRA), generated angiotensin I was trapped and quantitated by high affinity antibodies [19].

Calculation of renal parameters

Clearances (C), filtration fraction and fractional excretion were calculated by the traditional formula [14]. Fractional excretion (FE_x) was calculated as the clearance of x divided by the glomerular filtration rate. The coefficients of variation for two determinations of inulin and PAH clearances and FE_{Li} in the same conditions but at two week intervals were 5%, 13% and 20.3%, respectively ($N = 20$).

Statistical analysis

All results are expressed as mean ± 1 SEM. Differences were assessed by an analysis of covariance or an analysis of covariance followed by paired Student *t*-test when appropriate with a value of $P < 0.05$ as the level of significance. We looked for significant changes within and between the groups.

RESULTS

After one week of the diet, the two groups of ten volunteers were comparable in terms of age, body wt, systolic and diastolic BPs, heart rate and renal hemodynamics. In addition, the value of the last 24-hour urinary sodium excretion before the first drug administration were: 95 ± 11 mmol/day in the valsartan group, 91 ± 14 mmol/day in the valsartan + indomethacin group, and 80 ± 11 mmol/day in the enalapril and 88 ± 14 mmol/day in the enalapril + indomethacin group (P = NS between groups). There were no significant hemodynamic, biochemical or hormonal differences between the four treatment groups at baseline. The administration of valsartan, enalapril and indomethacin was well tolerated by all subjects, and no significant clinical or laboratory side effect was observed. Two subjects withdrew consent and were replaced.

Effects of indomethacin on the acute response to valsartan and enalapril

The effects of indomethacin on the acute hemodynamic and tubular effects of valsartan and enalapril are presented in Table 1. In these moderately salt-depleted subjects, both valsartan and enalapril induced a significant, transient decrease in diastolic BP with no change in systolic BP. The maximal change in pressure was observed four hours after drug intake with both agents. The decreases in diastolic BP were slightly less when valsartan and enalapril were co-administred with indomethacin, but the differences were not statistically significant.

Valsartan and enalapril had no significant effect on GFR nor did the co-administration of indomethacin, although a slight but nonsignificant decrease in GFR was noted two hours after the administration of indomethacin (Fig. 2A). In contrast, a significant increase in ERPF was observed with valsartan and enalapril. The maximal effect on ERPF was observed six hours after drug intake ($P = 0.005$ at 6 hr vs. baseline in the valsartan group and $P = 0.03$ at 6 hr in the enalapril group). Indomethacin did not affect the valsartan- and the enalapril-induced renal vasodilation (Fig. 2B). A slight decrease in filtration fraction was found both with valsartan and enalapril but only the changes induced by enalapril reached statistical significance (Table 1). No significant change in filtration fraction was found in the indomethacin-treated groups.

As shown in Figure 2C, similar significant increases in urinary sodium excretion were found both with valsartan and enalapril. Indomethacin equally abolished the natriuretic response to angiotensin II receptor blockade and ACE inhibition. Indeed, at two and four hours, the natriuretic response to valsartan was significantly blunted by indomethacin ($P = 0.004$ at 2 hr and $P = 0.025$ at 4 hr for valsartan vs. valsartan + indomethacin). A similar effect was found with enalapril ($P = 0.06$ at 2 hr and $P = 0.011$ at 4 hr, enalapril vs. enalapril + indomethacin). The cumulative six-hour sodium excretion was significantly reduced by the administration of indomethacin ($P = 0.013$, valsartan vs. valsartan + indomethacin, and $P = 0.009$, enalapril vs. enalapril + indomethacin). Urinary potassium excretion decreased significantly in all groups but no significant difference was found between the groups. The variations in FE_{Li} were not significant in the valsartan and enalapril groups. However, in the valsartan + indomethacin group, significant decreases in FE_{Li} were observed two and four hours after the administration of indomethacin ($P = 0.01$). The changes in FE_{Li} observed in the enalapril + indomethacin group was of equal magnitude but did not reach statistical significance.

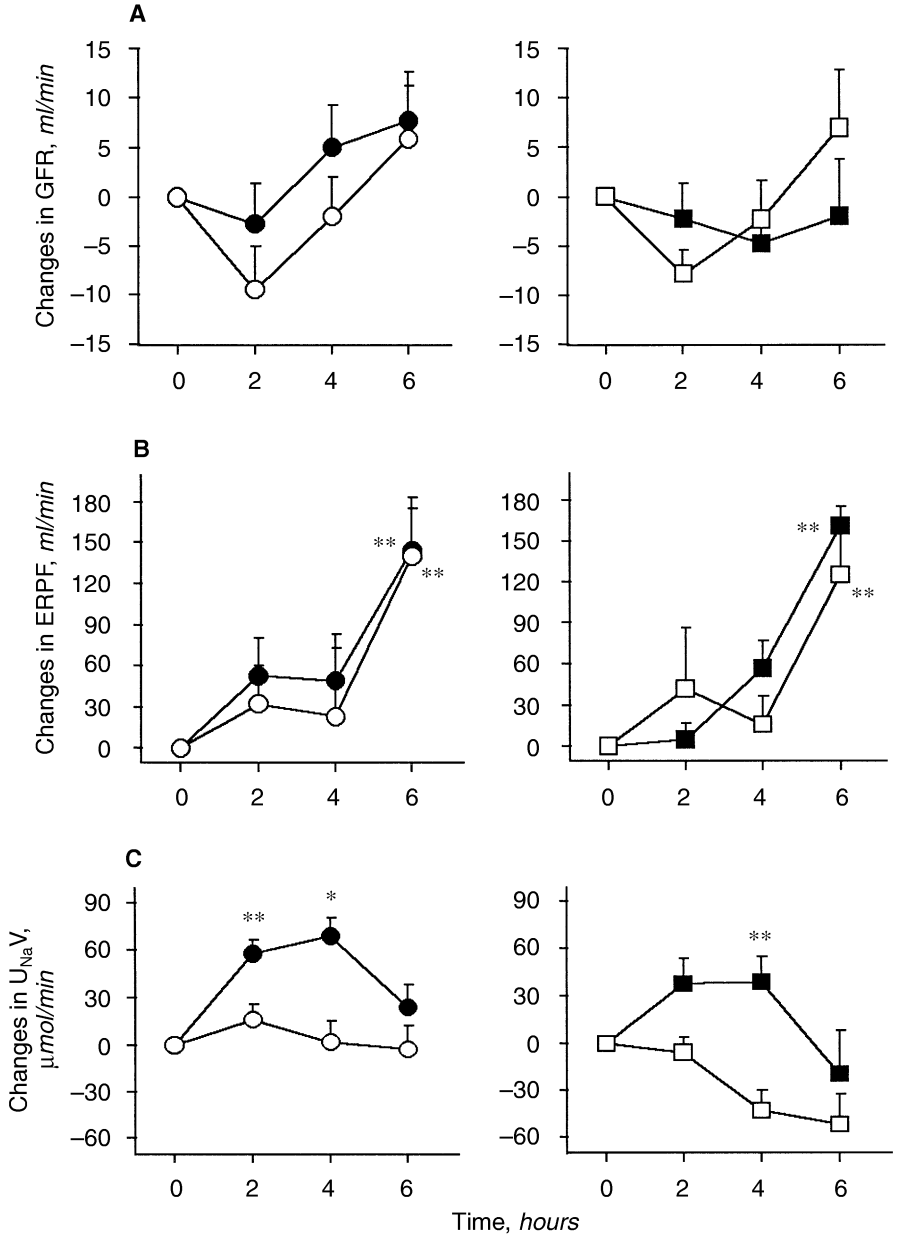

Fig. 2. Acute changes in glomerular filtration rate (GFR; *A*), effective renal plasma flow (ERPF; *B*) and urinary sodium excretion ($U_{Na}V$; *C*) induced by valsartan (●), valsartan + indomethacin (○), enalapril (■) and enalapril + indomethacin (□) on day 1. Values are means ± SEM; $^{*}P < 0.05$, $^{**}P < 0.01$ versus time 0.

Effects of indomethacin on the sustained renal response to valsartan and enalapril

After one week of valsartan and enalapril alone or combined with indomethacin, no significant change in blood pressure was found in the four treatment groups. From day 1 to day 7, supine plasma renin activity increased from 1.23 ± 0.2 to 3.0 ± 0.5 ng Ang I/ml/hr with valsartan ($P = 0.001$), from 1.02 ± 0.15 to 2.0 ± 0.45 with valsartan + indomethacin (P = ns), from 0.97 ± 0.15 to 3.2 ± 0.6 with enalapril ($P = 0.011$), and from 0.85 ± 0.08 to 2.6 ± 0.7 with enalapril + indomethacin (P = NS). Cumulative one week sodium excretion was slightly greater in the valsartan than in valsartan + indomethacin group (607 ± 25 vs. 581 ± 30 mmol/week, $P = 0.07$) and in the enalapril group as compared to the enalapril + indomethacin group (704 ± 39 vs. 635 ± 41 mmol/week, $P = 0.043$). After one week, sodium balance was not different in the valsartan + indomethacin and the enalapril + indomethacin groups. No significant change in cumulative potassium excretion was observed between the groups and cumulative creatinine excretion was comparable in all groups. Body weight decreased with valsartan and enalapril and remained slightly higher when indomethacin was added to either blocker of the renin-angiotensin system.

The effects of indomethacin on the renal response to angiotensin II receptor blockade and ACE inhibition on day 7 are shown in Table 2. No significant change in blood pressure, heart rate and GFR was observed after repeated

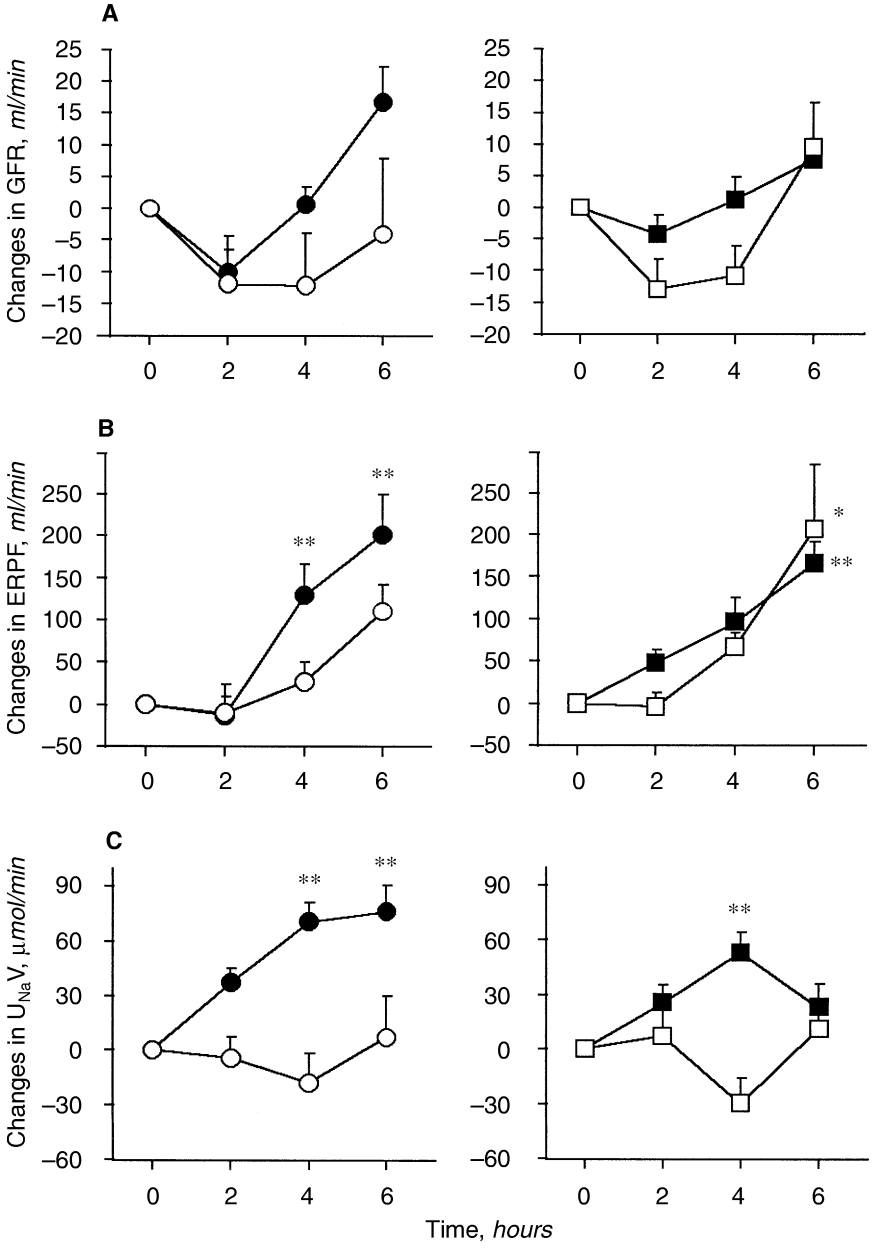

Fig. 3. Changes in GFR (*A*), ERPF (*B*) and urinary sodium excretion ($U_{Na}V$; *C*) induced by valsartan (●), valsartan + indomethacin (○), enalapril (■) and enalapril + indomethacin (□) on day 7. Values are means ± SEM; $^{*}P < 0.05$, $^{**}P < 0.01$ versus time 0.

administration of valsartan or enalapril alone or combined with indomethacin. As shown on Figure 3B, an equal increase in ERPF was again observed upon administration of valsartan and enalapril with a maximal effect at six hours ($P = 0.005$ baseline vs. 6 hr with valsartan and $P = 0.0001$ with enalapril). The coadministration of indomethacin appeared to blunt the renal vasodilatory effect of valsartan (P = NS, baseline vs. 6 hr in the valsartan + indomethacin group) but there was no significant difference between the valsartan and the valsartan + indomethacin groups. Indomethacin had no effect on the response to enalapril ($P = 0.02$ baseline vs. 6 hr in the enalapril + indomethacin). As observed on day 1, both the administration of valsartan and enalapril increased sodium excretion ($U_{Na}V$ and FE_{Na}) and this natriuretic response was again abolished by indomethacin (Fig. 3C). Potassium excretion decreased significantly in all four treatment groups. On day 7, no significant change in FE_{Li} was found within and between the groups.

DISCUSSION

This study demonstrates that the angiotensin II receptor antagonist valsartan and the ACE inhibitor enalapril have comparable acute and sustained renal hemodynamic and tubular effects, leading to significant increases in effective renal plasma plasma flow and urinary sodium excretion without affecting glomerular filtration rate. In addition, the

present data show for the first time, to our knowledge, in humans that the administration of a nonsteroidal anti-inflammatory agent abolishes the natriuretic, but not the renal hemodynamic response to angiotensin II receptor blockade. Since indomethacin similarly inhibits the natriuresis induced by valsartan and by enalapril, our results suggest that the antagonistic effect of NSAIDs is not class-specific.

Hemodynamic effects

During salt-depletion, blood pressure becomes renin-dependent and a fall in blood pressure can be expected when the renin-angiotensin system is blocked [20, 21]. In our moderately salt-restricted normotensive subjects, valsartan and enalapril indeed lowered diastolic blood pressure after the first dose and after one week of administration, blood pressure was still slightly but not significantly reduced. The rather modest degree of salt restriction and the difficulties to maintain a fixed sodium intake for almost two weeks certainly account for the absence of a persistent reduction in blood pressure during repeated administration. Although NSAIDs are known to produce mild elevations of blood pressure, particularly in hypertensive patients, the co-administration of indomethacin with valsartan and enalapril had no significant influence on blood pressure. This suggests that NSAIDs have only a minor impact on blood pressure in normotensive subjects who are on a relatively low sodium intake regimen. This hypothesis is supported by previous studies showing that ibuprofen and/or indomethacin have no effect on blood pressure in furosemide-treated normotensives [22] or in captopril-treated subjects [23]. Moreover, a recent meta-analysis has demonstrated that significant effects of NSAIDs on blood pressure are observed almost uniquely in hypertensive patients [24].

It is now well demonstrated that blockade of the renin-angiotensin system with ACE inhibitors, renin inhibitors and angiotensin II receptor antagonists enhances renal blood flow without affecting GFR [12–14, 25–28]. In agreement with these observations, we have found that both valsartan and enalapril increase effective renal plasma flow, whereas neither drug has an influence on GFR. Together with the renin-angiotensin system, prostaglandins appear to play a crucial role in maintaining an adequate renal perfusion during salt-depletion [1, 29]. Thus, NSAIDs have been shown to decrease renal blood flow and sometimes GFR in salt-depleted normotensive subjects [29]. However, this finding remains somewhat controversial. Indeed, many investigators have reported little if any effect of indomethacin on renal hemodynamics in salt-depleted [30, 31] and salt-repleted volunteers [32]. Whether prostaglandin synthase inhibitors modulate the renal hemodynamic effects of drugs inhibiting the renin-angiotensin system is also a matter of debate. In normotensive subjects, ibuprofen has been reported to blunt the captopril-induced increases in GFR and ERPF [23], but in hypertensive patients indomethacin had no effect on renal plasma flow and GFR when combined with trandolapril [33]. In our experience, indomethacin had no influence on the changes in renal hemodynamics induced by valsartan and enalapril. During repeated administration, the valsartan-induced renal vasodilation was slightly blunted by indomethacin, but the difference did not reach a relevant level of statistical significance.

Effects on urinary sodium excretion

Several studies in normotensive subjects have shown that ACE inhibitors or angiotensin II receptor antagonists increase urinary sodium excretion [25–28]. The results of the present study largely confirm this general observation, as both valsartan and enalapril equally increased urinary sodium excretion within the first six hours after drug intake. During repeated administration, a transient natriuretic response could still be demonstrated, mainly with valsartan. This observation is in accordance with our previous finding in normal subjects receiving irbesartan for one week [26]. Whether NSAIDs interfere with the natriuresis induced by angiotensin II receptor antagonists has, to our knowledge, not been studied in humans to date. Our results clearly indicate that indomethacin abolishes the natriuretic effect of valsartan leading to a significant reduction of the valsartan-induced six hour cumulative sodium excretion on day 1. After one week of indomethacin, the cumulative sodium excretion was still lower in the valsartan + indomethacin group than in the valsartan group, but the difference was less pronounced due the indidual variability. When combined with enalapril, the effect of indomethacin was comparable on the first day. During repeated administration, however, the effect on cumulative sodium excretion was slightly more pronounced. Yet, sodium balance was not different in the valsartan + indomethacin and in the enalapril + indomethacin groups, suggesting that indomethacin blunts the natriuresis induced by the angiotensin II receptor antagonist and the ACE inihibitor in a comparable way.

Our finding, that indomethacin attenuates the natriuretic effect of valsartan and enalapril similarly, provides some interesting new insights on the role of prostaglandins as potential mediators of the renal tubular effects of ACE inhibitors and angiotensin II receptor antagonists. Indeed, it has been postulated that ACE inhibitors may act by mechanisms other than inhibition of angiotensin II generation. ACE inhibitors are known to inhibit the enzyme that metabolizes bradykinin, which acts at least partly via the release of vasodilatory prostaglandins. In addition, ACE inhibitors may stimulate the production of prostaglandins, an effect that can be blocked by indomethacin [9, 10]. It has therefore been suggested that the effects of ACE inhibitors on renal tubular function is mediated in part by prostaglandins. In contrast to ACE inhibitors, angiotensin II receptor

antagonists have no influence on prostaglandins [15]. If prostaglandins mediate some of the effects of ACE inhibitors, one could expect that urinary electrolyte excretion differs during angiotensin II receptor blockade and ACE inhibition. Our results do not support this hypothesis, since comparable effects on sodium and potassium excretion were observed with valsartan and enalapril. Several recent studies have shown that ACE inhibitors and angiotensin II receptor antagonists have similar effects on blood pressure, renal hemodynamics, urinary protein and sodium excretion in hypertensive patients and normotensive subjects [12–14, 25, 26]. Thus, the interaction of the NSAID with the blockers of the renin-angiotensin system, valsartan and enalapril, more likely results from the fact that these drug classes have opposing effects on tubular sodium handling that are mutually attenuated by the addition of the other compound, as suggested earlier with ibuprofen and captopril [23]. Therefore, the interaction of NSAIDs with ACE inhibitors is probably not class-specific for the ACE inhibitors.

The ACE inhibitor-induced natriuresis appears to result from a decrease sodium reabsorption in the proximal segment of the nephron and via aldosterone reduction in distal segments [27, 28]. Similar observations have been reported with angiotensin II receptor antagonists although a direct effect on sodium handling by the proximal tubule has not always been demonstrated [25, 26]. In accordance with our previous observations using other angiotensin II antagonists, no clear effect of valsartan and enalapril on proximal sodium reabsorption was observed with valsartan as no significant change in lithium excretion was found. This suggests a prominent effect of these agents on distal sodium reabsorption in our experimental conditions [34]. The slight decrease in FE_{Li} observed four hours after the administration of valsartan and enalapril reflects the individual variability in lithium excretion. When both blockers of the renin-angiotensin system were combined with indomethacin, however, more pronounced decreases in FE_{Li} were found. This would indicate that indomethacin increases sodium reabsorption in the proximal segments of the nephron. This finding is in agreement with early observations suggesting that indomethacin promotes sodium reabsorption in the proximal tubule [35] and/or in the medullary thick ascending limb [36–38]. Whether a decrease in filtered load of sodium contributes to the antinatriuretis cannot be ascertained from our data, since only moderate and nonsignificant decreases in GFR were observed in our subjects.

Taken together, this study demonstrates that although angiotensin receptor antagonists do not affect prostaglandin metabolism, indomethacin abolishes the natriuretic response to valsartan without affecting its renal hemodynamic effects. The mechanism of the indomethacin-induced change appears to be nonspecific as the NSAID similarly blunts the natriuresis of the ACE inhibitor enalapril. Clinically, this pharmacodynamic interaction may be very important in patients with hypertension or congestive heart failure, as it may counteract the antihypertensive efficacy of these agents. Our observation in normotensive subjects may also be relevant for normotensive patients receiving ACE inhibitors or angiotensin II receptor antagonists to prevent the progression of renal diseases.

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Reprint requests to Dr. Michel Burnier, M.D., Division of Hypertension and Vascular Medicine, Department of Medicine, Policlinique Medicale Universitaire, Rue Cesar Roux 19, CHUV - 1011 Lausanne, Switzerland.
E-mail: Michel. Burnier@chuv.hospvd.ch

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